Autoimmune Derangement in a Patient with Simultaneous Diagnoses of Primary Anti phospholipid Syndrome, Thrombotic Thrombocytopenic Purpura and Heparin Induced Thrombocytopenia

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Abstract
Primary antiphospholipid syndrome (APS), thrombotic thrombocytopenic purpura (TTP) and heparin induced thrombocytopenia (HIT) are all hypercoagulable conditions characterized by thrombocytopenia and high risks of thrombosis. A severe form of APS, namely catastrophic antiphospholipid syndrome (CAPS), further shares features with TTP by the presence of microangiopathic hemolytic anemia characterized by schistocytes on the blood smear. CAPS and TTP may be co-existing and an underlying autoimmune association was postulated. Here we report a patient who presented with initial symptoms of APS, who then simultaneously developed TTP and HIT after being exposed to Clopidogrel and Heparin. Our case suggests that the autoimmune deregulation in APS predisposes the patient to other immune related conditions.

Keywords: Primary antiphospholipid syndrome; Thrombotic thrombocytopenic purpura; Heparin induced thrombocytopenia; Fondaparinux; Plasmapheresis

Case Report
A 47 year old female who had a history of spontaneous deep vein thrombosis (DVT) diagnosed 10 years ago presented for evaluation of left leg swelling for 4 days in May 2011, and was found to have extensive left lower extremity acute and chronic DVT. She was previously treated with placement of an inferior vena cava (IVC) filter and a short course of warfarin. A diagnostic workup was carried out for fever and epigastric pain. A diagnostic workup was performed and showed no thrombosis in the IVC, hepatic or portal veins. On day 14, the patient’s anemia and thrombocytopenia had continued to worsen, with Hgb 6.6 g/dl and platelet count 23,000/μl. In addition, a new renal insufficiency developed (creatinine was 1.9 mg/dl), and the peripheral smear now showed schistocytes. At this point, a differential diagnosis of thrombotic thrombocytopenic purpura (TTP) or catastrophic antiphospholipid syndrome (CAPS) was considered. Based on the time course of heparin and enoxaparin use, heparin induced thrombocytopenia (HIT) was also included in the differential diagnosis. On this day, confirmatory tests for TTP and HIT were drawn and sent to reference labs; Plasmapheresis was started; and fondaparinux was selected for anticoagulation while enoxaparin and clopidogrel were discontinued.

The patient's condition gradually improved after plasmapheresis with normalization of platelet count, PTT, hyperbilirubinemia and renal function (Figure 1). She was discharged on day 32 on warfarin. The confirmatory lab tests showed a severe deficiency in the von Willebrand factor (vWF) clearing protease activity (also known as ADAMTS-13) of less than 1% (68-163%). There was also a detection of a strong inhibitor of vWF clearing protease at 3.0 BEU (<0.5 BEU). In addition, a strong heparin induced platelet factor 4 antibody (Optic Density, O.D. 2.45) was detected by ELISA test. The Serotonin Release Assay (SRA), a gold standard for the laboratory diagnosis of HIT, was also strongly positive, showing serotonin release of 84% and 85% at low doses of unfractionated heparin (UFH) 0.1 IU/ml and 0.5 IU/ml (normal <20% for both), and 7% at high dose of UFH (positive if more than 50% reduction), confirming the diagnosis of HIT (Table 1).

Six weeks after discharge, her PTT became elevated again to 57 seconds while on coumadin. Four months after discharge her PTT was

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still elevated, and a repeat test of the antiphospholipid antibody panel demonstrated the presence of Lupus anticoagulant (LAC), elevated titers of anti-cardiolipin antibody IgG of 17 U/ml (normal <10) and anti-phosphatidyserine antibody IgG of 43 U/ml (normal <10).

Discussion

We show in this case report an interesting case which illustrates that one patient was diagnosed of APS, TTP and HIT simultaneously under a clinical condition where she was treated with heparin, enoxaparin and clopidogrel [1,2]. As all of the above three diagnostic conditions were confirmed by laboratory tests, we discuss below whether those abnormal tests were only bystander effects of the presenting condition of APS, or were manifestations of true APS, TTP and HIT clinical conditions. In addition, we attempt to reason what could be the underlying driver for all those abnormalities.

The patient's presenting symptoms of spontaneous DVT, elevated baseline PTT, mild thrombocytopenia and the presence of LAC were consistent with the diagnosis of primary antiphospholipid syndrome (APS) [3]. However, at the time of presentation, these symptoms were new for this patient; an APS diagnosis could not be firmly made awaiting a repeat test that was supposed to be done 12 weeks later [3].

With a longer follow up, PTT elevation reappeared at 6 weeks after discharge and persisted at 4 months after discharge, which proved to be due to the presence of LAC. At the 4 months point, the diagnosis criteria of APS were met (Sapporo Criteria, ref 3), based on her DVT at occurrence, repeated detection of LAC, and elevated titers of anti-cardiolipin antibody and anti-phosphatidyserine antibody (Table 1). These repeated tests confirmed that the patient had primary APS at the time of presentation, and APS was the hypercoagulable status that led to her DVT.

When the patient’s anemia and thrombocytopenia worsened, the presence of schistocytes indicated microangiopathic hemolysis, which can be seen in both TTP and catastrophic antiphospholipid syndrome (CAPS). The distinction of these two conditions can be very difficult [4], and it is also possible that CAPS can be associated with, or predispose to TTP [2,5]. In this case, the TTP diagnosis was ultimately confirmed by an extremely low vWF cleaving protease activity of <1% and the detection of a strong inhibitor to vWF cleaving protease [6-8]. Of note, a mildly decreased vWF cleaving protease activity has been reported in multiple conditions including HIT [9] and Systemic Lupus Erythematosus (SLE) [10]; however, a markedly low vWF cleaving protease activity is highly specific for TTP, even in the presence of primary APS [2].

Our patient was exposed to clopidogrel for 7 days. As the appearance of TTP like symptoms and signs occurred after 4-5 days of clopidogrel use, it was highly likely that clopidogrel was the direct cause of TTP [11]. The detection of a strong inhibitor of vWF cleaving protease indicates the development of an inhibitory autoantibody, which is consistent with the previous described mechanism of clopidogrel induced TTP [8].

The time course of the progression the patient's thrombocytopenia was consistent with HIT. However, since DVT happened before heparin use, it therefore cannot be used in the “4T” diagnostic criteria developed for HIT pretest prediction [12]. By the “4T” criteria [12], the pretest probability of HIT was intermediate with a score of 5. In addition, the worsening of thrombocytopenia and decline of renal function were not consistent with HIT. There were also no obvious signs of new DVT or progression of DVT while the patient was continued on Enoxaparin from day 8 to day 13. In the presence of competing causes for thrombocytopenia such as TTP, HIT testing is not routinely recommended [12]. Nevertheless, a diagnosis of HIT was strongly supported by both ELISA and SRA assays; the latter is highly specific and considered a gold standard for the diagnosis of HIT [13]. Could the presence of heparin induced platelet factor 4 antibody in this complicated case a bystander effect due to APS? It is known that a low titer of heparin platelet factor 4 antibodies can be detected in a few patients with APS who have never been exposed to heparin [14,15], and the HIT antibody may even elicit a positive SRA in some cases [15]. However, in those previous studies, those HIT antibodies were weak and of low titer, typically with O.D. values of less than 0.8 [15], far lower than the strong O.D. of 2.45 in our patient. The high titer of heparin platelet factor 4 antibodies and highly positive result from the SRA assay in this patient indicates immune augmentation in response to heparin exposure, therefore supporting a clinical diagnosis of simultaneous HIT. This question might be better answered if a baseline titer of heparin associated platelet 4 antibody prior to heparin exposure was available. Clinically the patient did not have progression of her
DVT because the right choice of anticoagulation drug was selected.

The presence of an array of auto-antibodies associated with three critical conditions, namely APS, TTP, and HIT in this patient with recurrent DVT suggests that the development of those antibodies was not random, and the association of these diagnoses was not by chance. We hypothesize that an underlying autoimmune disorder in this patient might have had a low titer of those antibodies associated with APS, TTP, and HIT respectively. The patient manifested a deranged, augmented B cell antibody response to exposed stimuli or antigens, in this case, clopidogrel and heparin. The patient might have had a low titer of those antibodies associated with APS, TTP, and HIT. This case underscores the importance of considering both diagnoses of TTP and HIT despite an intermediate pretest score, particularly in patients who have autoimmune conditions of TTP and HIT. This case underscores the importance of preclinical and when the choice of anticoagulation is crucial.

We believe that this is the first report in the literature that shows simultaneous development of TTP and HIT in a patient with APS. The presumed autoimmune derangement warrants further preclinical and clinical investigation.

### Table 1: Supportive lab results

<table>
<thead>
<tr>
<th>Test name</th>
<th>Test result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin PF4 antibody ELISA</td>
<td>Positive</td>
<td>O.D. &lt;1.0</td>
</tr>
<tr>
<td>Serotonin Release Assay</td>
<td>Negative</td>
<td>normal &lt;20% at both low dose heparin levels</td>
</tr>
<tr>
<td>VWF protease activity (ADAMTS 13)</td>
<td>&lt;1%</td>
<td>68-163%</td>
</tr>
<tr>
<td>VWF protease inhibitor</td>
<td>3.0 BEU</td>
<td>&lt;0.4 BEU</td>
</tr>
<tr>
<td>Lupus Anticoagulant (DRVVT)</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>Anti cardiopipin IgG Ab</td>
<td>Detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>Phosphatidyserine Ig G Ab</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

### References


